

## REMARKS

Upon entry of these amendments, claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53, and 73-76 are pending in the instant application. Claims 55-72 are cancelled as directed to non-elected subject matter. Applicant reserve the right to pursue the subject matter of these claims in one or more continuing applications. Claims 1, 35, 73 and 74 are amended for language clarification. Claims 75 and 76 are added. Support for these new claims can be found in claims 1 and 35 as originally filed. No new matter is added.

### **Objections to the Claims**

Claims 1 and 35 are objected to for reciting the phrase “effect the viability of,” which the Examiner states is grammatically awkward and should read -- affect the viability thereof -- for clarity. Claims 1 and 35 are amended as requested by the Examiner. Applicants request withdrawal of the objection.

Claims 35, 38-39 and 43-51 are objected to under 37 C.F.R. 1.75 as being substantial duplicates of present claims 1, 4-5 and 9-17, respectively. Examiner states, “When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight different in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. Please reference MPEP §706.03(k).” Claim 35, from which the remaining claims subject to the rejection depend, is amended to clarify the invention. Applicants submit that claim 35 as amended is not duplicative of claim 1 and as such request withdrawal of the objection.

### **35 U.S.C. §112, First Paragraph, Written Description Requirement**

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53, and 73-74 are rejected under 35 U.S.C. §112, first paragraph, as filing to comply with the written description requirement. Specifically, the Examiner states that the instant specification fails to provide written support for the concept of elevating any E2F-1, E2F-2 or E2F-3 using any G1 and/or S phase checkpoint activator. *See*, Office Action at pages 3-4. Further, the Examiner states that the instant specification fails to

provide adequate written description for a genus of G1 and/or S phase checkpoint activators or the genus of orthonaphthoquinones as checkpoint activators. *See*, Office Action at pages 4-8. Applicants traverse.

Applicants submit that the instant specification describes a representative number of species of G1 and/or S phase checkpoint activators and orthonaphthoquinones. The instant specification describes that the orthonaphthoquinone family is a preferred genus of G1 and/or S phase checkpoint activators, further describes that analogs and derivatives of  $\beta$ -lapachone are preferred orthonaphthoquinone compounds. *See*, for example, specification at page 15, lines 15-18, and page 12, line 25-34, respectively, and U.S. Patent Publications 2002/0169135 and 2003/0091639 recited at page 12, lines 21-23 and page 13, lines 16-18, respectively, and incorporated by reference in the instant application. Moreover, the instant specification provides working examples, demonstrating reduction to practice, for three specific orthonaphthoquinone compounds: 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho[1,2-b]pyran-5,6-dione, 3,4-dihydro-2,2-dimethyl-2H-naphtho[1,2-b]thiopyran-5,6-dione and 3,4-dihydro-4,4-dimethyl-2H-naphtho[1,2-b]thiopyran-5,6-dione demonstrating how these specific compounds elevate the expression of E2F-1, E2F-2 or E2F-3 in cancer cells. *See*, for example, specification at page 9, lines 17-29 to page 10, lines 1-28 (description of drawings) and pages 30-37 (examples and drawings).

Applicants submit that the instant specification provides chemical formula and names and the physical properties for these genus and that the disclosure indicates that Applicants have invented species sufficient to constitute the genus and as such satisfies the standards in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). *Lilly* requires that the instant specification recite structural features common to members of the genus. *Enzo* requires that the specification disclose the relevant identifying characteristics of the genus, functional characteristics of the genus coupled with a disclosed correlation between structure and function or some combination of such characteristics.

Applicants submit that one of ordinary skill in the art would readily recognize the core structural features common to the orthonaphthoquinone genus based on the disclosure of the

instant invention and the disclosures of U.S. Patent Publications 2002/0169135 and 2003/0091639 recited at page 12, lines 21-23 and page 13, lines 16-18, respectively, and incorporated by reference in the instant application. The instant specification provides working examples that demonstrate, and reduce to practice, that these common structural features are essential to the claimed function of the compounds of the genus, *i.e.*, to elevate the expression of a member of the E2F family of transcription factors and to activate a G1 and/or S phase checkpoint in cancerous cells, without affecting the viability of non-cancerous cells. *See*, for example, specification at pages 9-10 and 30-36 for a description of figures 2, 3, 5, 7, and 11, which show a selective apoptotic effect on cancer cells; figures 8, 9, 10, and 11, which show an elevation of E2F-1 protein levels in response to treatment with the checkpoint activator; and figure 11 which demonstrates both a selectivity for cancer cells and a resulting elevation in E2F-1 protein.

Thus, Applicants submit that one of ordinary skill in the art reading the instant specification would readily recognize that the instant specification conveyed at the time of filing that Applicants were in possession of the invention as claimed herein. Withdrawal of this rejection is respectfully requested.

### **35 U.S.C. §112, First Paragraph, Enablement**

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53, and 73-74 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the administration of a G1 and/or S phase checkpoint activator selected from 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho[1,2-b]pyran-5,6-dione, 3,4-dihydro-2,2-dimethyl-2H-naphtho[1,2-b]thiopyran-5,6-dione, 3,4-dihydro-4,4-dimethyl-2H-naphtho[1,2-b]thiopyran-5,6-dione, or beta-lapachone, for the treatment of prostate, colon, breast, pancreatic or lung cancer in an amount effective to cause tumor regression, does not reasonably provide enablement for the administration of a dose that selectively activates a checkpoint in cancerous cells while elevating the expression of an E2F transcription factor selected from the group consisting of E2F-1, E2F-2, or E2F-3 but not affecting the viability of non-cancerous cells in said subject, for the reasons set forth at pages 5-9 of the Office Action dated August 29, 2006. The Examiner further states that

although Applicant's amendments removing the limitation directed to the determination of the appropriate dosage of the checkpoint activator have been noted, such an amendment does not remedy the fact that Applicant provides no guidance or direction as to the manner and process by which one of ordinary skill in the art would go about determining those dosage amounts of checkpoint activator that are effective to elevate E2F expression but do not affect non-cancerous cells. *See*, Office Action at pages 9-11. Applicants traverse.

Applicants submit that the instant application provides adequate direction to one of ordinary skill in the art at the time of the invention to determine what dosage amounts are effective to achieve the objective of elevated E2F expression with no toxic effect on non-cancerous cells without placing a burden of undue experimentation upon the skill artisan.

The application provides therapeutically effective dosage ranges for use in the instant invention at page 29, line 26, to page 30, line 6. Further, the instant specification provides adequate guidance and protocols in Examples 1-3 at pages 30-37 such that one of ordinary skill in the art would readily be able to determine the amount necessary to administer to elevate E2F expression without affecting non-cancerous cell viability. Moreover, Applicants submit that determining the specific amount necessary to administer for a specific subject is well within the art of the appropriate clinician or practitioner in view of the instant application. Reconsideration and withdrawal are respectfully requested.

### **35 U.S.C. §112, Second Paragraph**

Claims 1, 4-5, 10-17, 35, 38-39, 43-51, 53, and 73-74 are rejected under 35 U.S.C. §112, second paragraph. The Examiner states, "In particular, Applicant's limitation directed to "a G1 and/or S phase checkpoint activator" does not clearly or deliberately set forth exactly what compounds are to be administered in the context of the claimed method....the and/or conjunction that is present in the claim does not precisely set forth the metes and bounds of the genus of checkpoint activators intended to be within the scope of the method." *See*, Office Action at page 12.

Applicants disagree. However, in the interest of expediting prosecution, claims 1, 35 and 53 (from which the remaining claims subject to the rejection depend) are amended to recite "a

G1 or S phase checkpoint activator.” As such, Applicants respectfully request withdrawal of the instant rejection.

Claims 1, 4-5, 10-17, 35, 38-39, 44-51, and 73-74 are also rejected under 35 U.S.C. §112, second paragraph. The Examiner states “recitation of the limitation selectively activate a checkpoint in cancerous cells is inconsistent with the function of the compounds to be administered. The Examiner also states, “there are limited functions attributed to the claimed activators such that the recitation of activating “a checkpoint” is inconsistent with the claimed G1 and/or S phase activating function of the claimed compounds because it does not specifically refer back to the checkpoints previously recited in the claim....it is not clear whether Applicant intends to activate G1 and/or S phase, or any other cell cycle checkpoint.” *See*, Office Action at page 13.

Applicants disagree. However, in the interest of expediting prosecution, claims 1, 35 and 53 (from which the remaining claims subject to the rejection depend) are amended to recite “activate a G1 or S phase checkpoint.” Claims 1 and 35 are also amended to delete the term “selectively.” As such, Applicants respectfully request withdrawal of the instant rejection.

Claims 73-74 are rejected under 35 U.S.C. §112, second paragraph. The Examiner states, “In particular, there is insufficient antecedent basis for the limitation “said compound” in present claims 73-74, since any reference to such a “compound” is noticeably absent from the claim from which these depend (i.e. claim 1).”

Claims 73 and 74 are amended to recite, “, wherein said checkpoint activator is an orthonaphthoquinone.” As such, Applicants request reconsideration and withdrawal of the present rejection.

### **35 U.S.C. §102**

Claims 1, 4-5, 10-17, 35, 38-39, 43-51, 53, and 73-74 are rejected under 35 U.S.C. §102(a) as being anticipated by WO 03/01124 to Jiang et al. ( “Jiang”) in light of Jacob et al., “Paclitaxel,” Pharmacology, 4<sup>th</sup> Ed., 1996; p. 268 (“Jacob”), cited to show a fact. *See*, Office

Action at pages 14-17. Applicants traverse the rejection with respect to the claims as amended herein.

Claims 1, 35 and 53 (from which the remaining claims subject to the rejection depend) are amended to recite that the G1 or S phase checkpoint activator is administered to activate a G1 or S phase checkpoint in cancerous cells and induce apoptosis in cancer cells but where the activator is not toxic to and does not affect the viability of non-cancerous cells. Claims 1 and 35 are further amended to recite that the G1 or S phase checkpoint activator is administered to elevate the expression of a member of the E2F family of transcription factors and E2F-1, respectively.

Jiang does not teach or suggest, explicitly or inherently, the administration of a G1 or S phase checkpoint activator which will induce apoptosis in cancerous cells without affecting the viability of non-cancerous cells and does not teach or suggest the administration of a G1 or S phase checkpoint activator to elevate the expression of a member of the E2F family of transcription factors, as required by the instant claims. Applicants respectfully request consideration and withdrawal of the present rejection.

### 35 U.S.C. §103

Claims 1, 15-17, 35, and 49-51 are rejected under 35 U.S.C. §103(a) as being unpatentable over Jiang in view of WO 00/61142 to Pardee (“Pardee”). Applicants traverse the rejection with respect to the claims as amended herein.

Claims 1 and 35 (from which the remaining claims subject to the rejection depend) are amended to recite that the G1 or S phase checkpoint activator is administered to activate a G1 or S phase checkpoint in cancerous cells but where the activator is not toxic to and does not affect the viability of non-cancerous cells. Claims 1 and 35 are further amended to recite that the G1 or S phase checkpoint activator is administered to elevate the expression of a member of the E2F family of transcription factors and E2F-1, respectively.

As described *supra*, Jiang does not teach or suggest, explicitly or inherently, the administration of a G1 or S phase checkpoint activator which will induce apoptosis in cancerous cells without affecting the viability of non-cancerous cells and does not teach or suggest the

administration of a G1 or S phase checkpoint activator to elevate the expression of a member of the E2F family of transcription factors, as required by the instant claims.

Pardee does not cure the deficiencies of Jiang. Pardee merely teaches the administration of G1 and/or S phase drugs in combination with a variety of G2/M phase drugs for the treatment of various cancers. Pardee does not teach or suggest the administration of a G1 or S phase checkpoint activator to elevate the expression of a member of the E2F family of transcription factors to induce apoptosis in cancerous cells without affecting the viability of non-cancerous cells, as required by the instant claims. As such, one of ordinary skill in the art would be unable to combine Jiang and Pardee to reach the claimed invention. Applicants respectfully request consideration and withdrawal of the present rejection.

#### **Obviousness-Type Double Patenting, Provisional Rejections**

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53, and 73-74 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims contained within U.S. Patent Application Nos. 10/866,751; 10/887,009; 10/995,565; 11/068,459; 11/069,637; and 11/201,097, each already of record, for the reasons set forth at pages 3-5 of the Office Action dated January 17, 2006 and at pages 13-15 of the previous Office Action dated August 29, 2006, of which said reasons are herein incorporated by reference.

Applicants will consider filing a terminal disclaimer upon notice of allowable subject matter in these applications or the instant application.

#### **Obviousness-Type Double Patenting, Non-Provisional Rejections**

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53, and 73-74 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the method claims of U.S. Patent Nos. 6,245,807; 6,664,288; and 6,875,745. This rejection is directed solely to the claims of the above-cited patents that define methods of use, i.e., the same statutory category of invention. Applicants traverse the rejection with respect to the claims as amended herein.

The method of use claims within U.S. Patent No. 6,245,807 (“807”) are drawn to “A method of treating androgen independent prostate cancer” (Claim 1) and “A method of treating benign prostate hyperplasia” (Claim 2) by “administering to said human an effective amount of a compound of the following formulae I or II to stimulate prostate cell death” (Claims 1 and 2) wherein the claimed formulae I and II are chemical modifications of  $\beta$ -lapachone..

The method of use claim 1 of U.S. Patent No. 6,664,288 (“288”) is drawn to “A method of treating a mammal having a solid tumor (or tumors) formed as a result of a cancer selected from the group consisting of melanoma, colon cancer, prostate cancer, lung cancer, pancreatic cancer, ovarian cancer and breast cancer, the method comprising: a) administering to the mammal an effective amount of a first compound comprising .beta.-lapachone or derivatives thereof as the active ingredient; and b) administering to the mammal an effective amount of a G2/M phase drug.

Independent method of use Claims 4-5 of U.S. Patent No. 6, 875, 745 (“745”) are drawn to “A method of treating a solid tumor or tumors in a mammal in need thereof, the method comprising: a) administering to the mammal an effective amount of a first compound comprising .beta.-lapachone or a derivative or analog thereof as the active ingredient; and b) administering to the mammal an effective amount of a G2/M phase drug.... wherein the G2/M phase drug is selected from the group consisting of microtubule targeting and topoisomerase poison drugs.”

Claims 1, 35 and 53 (from which the remaining claims subject to the rejection depend) are amended to recite that the G1 or S phase checkpoint activator is administered to activate a G1 or S phase checkpoint in cancerous cells and induce apoptosis in cancer cells but where the activator is not toxic to and does not affect the viability of non-cancerous cells. Claims 1 and 35 are further amended to recite that the G1 or S phase checkpoint activator is administered to elevate the expression of a member of the E2F family of transcription factors and E2F-1, respectively.

The ‘807, ‘288 and ‘745 patents do not teach or suggest, explicitly or inherently, the administration of a G1 or S phase checkpoint activator which will induce apoptosis in cancerous cells without affecting the viability of non-cancerous cells and does not teach or suggest the administration of a G1 or S phase checkpoint activator to elevate the expression of a member of

the E2F family of transcription factors, as required by the instant claims. Applicants respectfully request consideration and withdrawal of the present rejection.

## CONCLUSION

On the basis of the foregoing amendment and remark, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



Ivor R. Elrifi, Reg. No. 39,529  
Matthew Pavao, Reg. No. 50,572  
Attorneys for Applicants  
c/o MINTZ, LEVIN  
Tel: (617) 542-6000  
Fax: (617) 542-2241  
**Customer No.: 30623**

Dated: September 24, 2007

ACTIVE 4106629v.1